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Changes in frailty among ICU survivors and associated factors: Results of a one-year prospective cohort study using the Dutch Clinical Frailty Scale

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ABSTRACT

Purpose: Frailty is an important predictor for the prognosis of intensive care unit (ICU) patients. This study examined changes in frailty in the year after ICU admission, and its associated factors.

Materials and methods: Prospective cohort study including adult ICU patients admitted between July 2016–December 2017. Frailty was measured using the Clinical Frailty Scale (CFS), before ICU admission, at hospital discharge, and three and 12 months after ICU admission. Multivariable linear regression was used to explore factors associated with frailty changes.

Results: Frailty levels changed among 1300 ICU survivors, with higher levels at hospital discharge and lower levels in the following months. After one year were 42% of the unplanned, and 27% of the planned patients more frail. For both groups were older age, longer hospital length of stay, and discharge location associated with being more frail. Male sex, higher education level and mechanical ventilation were associated with being less frail in the planned patients.

Conclusion: One year after ICU admission, 42% and 27% of the unplanned and planned ICU patients, respectively, were more frail. Insight in the associated factors will help to identify patients at risk, and may help in informing patients and their family members.

Registration: ClinicalTrials.gov database (NCT03246334).

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1. Introduction

Long-term physical, mental and cognitive health problems are common among patients who survived their intensive care unit (ICU) stay [1–3]. The underlying causes of these long-term problems are not fully understood, although they are generally thought to result from a complex relationship between the severity of critical illness, ICU treatment, post-ICU factors, and patient's pre-existing health, including the presence of comorbidities and frailty [4–6].

Frailty can be seen as a reflection of overall function. It is a recognizable state of increased vulnerability, due to decline in reserve and function, comprising the ability to cope with every day or acute stressors [7]. Frailty is characterized by a combination of decreased mobility and activity, weakness, reduced muscle mass, poor nutritional status and diminished cognitive function [7–9]. There is a bidirectional relation between frailty and critical illness: frailty is a risk factor for critical illness [1], but critical illness may also lead to frailty [10], because the frailty deficits of weight loss, undernutrition, muscle wasting and weakness can develop or worsen rapidly in critically ill patients, regardless of the specific critical illness diagnosis [11]. Frail ICU patients are more susceptible to adverse events, such as infections, and have a higher risk of ICU-, hospital- and long-term mortality compared to non-frail patients [4,7–9,12,13]. After hospital discharge, frail patients are more functionally dependent, and have more disabilities, a lower quality of life, and a worse psychosocial and physical recovery compared to those who are not frail [4,9–12,14]. Besides, frailty significantly impact healthcare utilization, due to unplanned hospital (re)admissions, increased ICU and hospital length of stay, and institutionalization [7–9,15].

Consequently, frailty has become an important predictor for the prognosis of critically ill patients [7,14]. Therefore, it is suggested to screen for frailty at ICU admission, to identify patients who are at risk, to provide clinicians with prognostic information and to help informed decision making with patients and families [7,11]. However, frailty should be considered as a dynamic state as changes in frailty are common [16], and is believed to be manageable and even potentially reversible, through targeted interventions such as exercise and nutrition

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[4,11,17]. Understanding of frailty changes during and after the ICU may help the decision making about interventions to prevent frailty among individuals at risk, and to reduce the vulnerability among those who are frail. Changes in frailty have often been investigated in community-dwelling older people [18]. However, to our knowledge, changes in frailty in ICU patients and factors associated with these changes have never been examined.

Therefore, the aims of this study were 1) to examine differences between frail and non-frail patients before ICU admission; 2) to determine changes in frailty in the year after ICU admission; and 3) to explore which factors were associated with changes in frailty.

2. Methods

2.1. Study design and participants

Data from one university medical centre were obtained from an ongoing multicentre prospective cohort study (MONITOR-IC study), in which long-term outcomes of ICU patients are assessed up to five years after ICU admission (ClinicalTrials.gov: NCT03246334). Patients were included when they were 16 years or older, expected to survive the ICU, and admitted for at least 12 h to the ICU between July 11, 2016 and December 31, 2017. Patient were excluded when they had a life expectancy of <48 h, or could not read and speak the Dutch language.

Information regarding the MONITOR-IC study, such as outcome measures and used instruments, are previously published in detail [19]. The study has been approved by the research ethics committee of the Radboud University Medical Center, CMO region Arnhem-Nijmegen (2016–2724). All patients, or their legal representative, provided written informed consent.

2.2. Data collection

Frailty was assessed using the Dutch Clinical Frailty Scale (CFS) [20] (for the English and Dutch CFS see Supplement 1 and 2 respectively). A description of the translation process can be found in Supplement 3. The CFS is a nine-item scale with pictographs and a description of the frailty domains, cognition, mobility, function and comorbidities [21,22], of which the score ranges from 1 ('Very fit') to 9 ('Terminally ill'). Patients were classified as 'Non-frail' (CFS score 1–4) or 'Frail' (score 5–9) [7].

Patients, or proxies in case patients were not able to fill in the questionnaire by themselves, were asked to rate their frailty by completing a self-administrated paper-based or online questionnaire (depending on their preferences) the day before ICU admission (T0), at hospital discharge (T1), and three (T2) and 12 months (T3) after ICU admission. The baseline questionnaire (T0), in which patients were asked to rate their health before ICU admission, was provided when patients were asked for informed consent. This was before ICU admission for planned admissions, and as soon as possible after ICU admission for unplanned admissions. Then patients were asked to rate their health retrospectively, recalling their situation before the ICU admission. Telephone and e-mail reminders were used in case of nonresponse.

Patient's demographics, including age, gender, education level, marital status and household composition were retrieved from the baseline questionnaire. Chronic diagnosis, admission type (classified as elective surgical, medical or acute surgical), planned admission, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, mechanical ventilation days, and ICU and hospital length of stay (LOS) were retrieved from the patient's electronic health record. Hospital discharge location was retrieved from the T1 questionnaire.

2.3. Statistical analysis

Baseline characteristics were presented as means with standard deviations (SD) for normally distributed continuous variables, medians with inter-quartile ranges (IQR) for not-normally distributed continuous variables, and counts with percentages for categorical variables. Differences in characteristics between non-frail and frail patients were analysed by using the independent-samples *t*-test or Mann-Whitney test for respectively normally distributed and not-normally distributed variables, and chi-square test or Fisher's exact test for categorical variables.

To explore which factors were associated with changes in frailty 12 months after ICU admission, linear regression analyses were performed. The dependent variable was the frailty change score, which was created by subtracting the CFS score of T0 from the T3 score for each patient. All patient variables (age, gender, education, marital status, household composition and chronic diagnosis) and ICU variables (admission type, APACHE IV score, mechanical ventilation, ICU LOS, hospital LOS and discharge location), were entered in a multivariable linear regression model. Normal distribution of residuals was checked using histograms and normal probability plots, and the homogeneity of variance (homoscedasticity) using a plot of standardized residuals versus predicted values. Multicollinearity was assessed using the indicators Variance Inflation Factor (VIF) and Tolerance statistics, with a score of >10 and a value <0.1 respectively, as an indication for multicollinearity. There was a strong correlation between the variables 'days of mechanical ventilation' and 'ICU LOS'. Therefore, the variable 'days of mechanical ventilation' was replaced by the variable 'mechanically ventilated (yes/no)'. Outliers were tested using the standardized residuals. Cooks' distance (<1) was used to determine if outliers had a significant influence on the model [23]. No significant outliers were found.

Because the majority of the included patients had a planned ICU admission, mainly after elective surgery, the analysis were performed for planned and unplanned patients separately.

Complete-cases (patients that completed both the CFS T0 and T3 questionnaire), were included in the linear regression analyses. Patient- and ICU characteristics were compared between complete-cases and non-responders (patients that filled in the T0, but not the T3), and complete-cases and non-survivors (patients that filled in the T0 and died within one year after ICU admission). All statistical analyses were performed using SPSS IBM statistical software (version 25). Values of $p < .05$ were considered statistically significant.

3. Results

3.1. Study population

In total, 2922 patients were admitted to the ICU of the university medical centre, of which 1760 patients were included in the study (Fig. 1). The most common reasons for exclusion were deceased before informed consent ($n = 210$), ICU LOS <12 h ($n = 163$) or a life expectancy of <48 h ($n = 140$). After informed consent, 460 patients dropped out, mainly because of not completing the baseline questionnaire ($n = 183$) and redrawing from study participation ($n = 122$) (Fig. 1). The response rates at hospital discharge, three and 12 months after ICU admission were 90% ($n = 1170$), 76% ($n = 991$) and 65% ($n = 846$) respectively.

The baseline questionnaire was completed by 1300 patients with a mean (SD) age of 61 (14.9) years, 65% ($n = 843$) were male, and 26% ($n = 337$) had one or more chronic diagnoses before admission. Median ICU and hospital LOS were 1 [IQR 1–2] and 9 [IQR 6–15] days respectively (Table 1). At baseline, 20% ($n = 257$) of the questionnaires were completed by proxies, which decreased to 7% ($n = 57$) at 12 months after ICU admission. Two-third of the patients ($n = 853$) had a planned ICU admission, and differed significantly from patients with a unplanned ICU admission ($n = 447$) (Supplement 4): patients with a planned admission were for example older, had a shorter ICU and hospital LOS, and had lower hospital and one-year mortality rates, compared to patients with an unplanned ICU admission.

Complete cases ($n = 846$) differed significantly from non-responders ($n = 338$): non responders were more often younger ($p < .001$), female ($p = .009$), lower educated ($p < .001$), and living alone

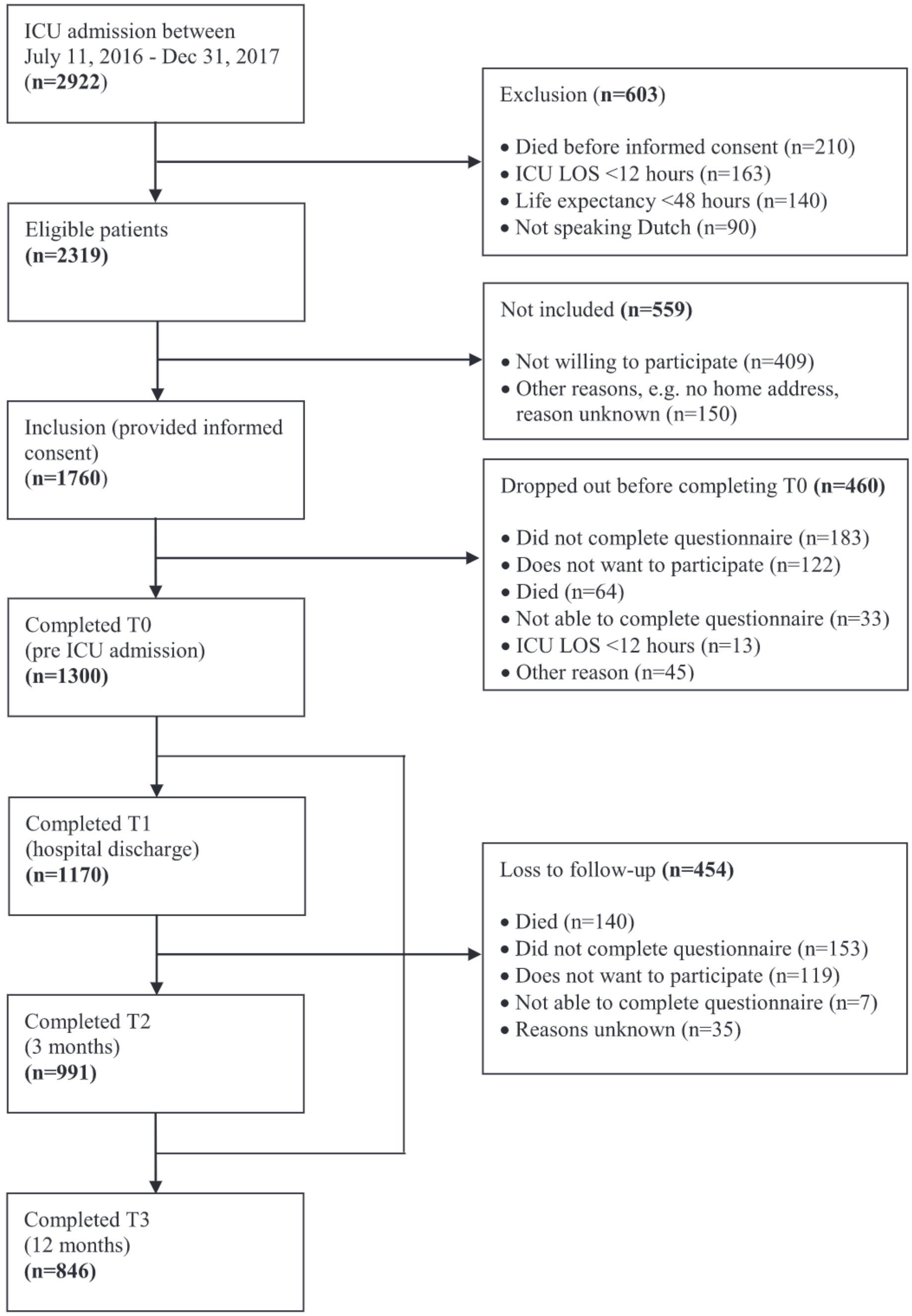


Fig. 1. Flow diagram of the study population. ICU: intensive care unit; LOS: length of stay; T0: before ICU admission; T1: at hospital discharge; T2: three months after ICU admission; T3: 12 months after ICU admission.

($p = .001$). Their CFS baseline score (median 3 [IQR 2–4]) tended to be higher ($p = .062$) (Supplement 5, Table 1). Also non-survivors ($n = 116$) differed significantly from complete-cases: non-survivors were for instance more often frail ($p = .007$), older ($p = .006$), living in a healthcare facility before admission ($p = .002$), suffering from chronic diagnoses ($p < .001$), had a higher APACHE IV score ($p < .001$), and longer ICU and hospital LOS ($p < .001$) (Supplement 5, Table 2).

3.2. Frailty before ICU admission and differences between frail and non-frail patients

The median CFS baseline score among patients with an unplanned ICU admission was 2 [IQR 2–4], representing a state of 'well', 16% of the patients ($n = 72$) were frail and 84% ($n = 375$) non-frail. Among patients with a planned ICU admission, the median CFS baseline score was 3 [IQR 2–3.5] (Supplement 4), but less patients were frail (10%, $n = 81$). None of the patients in both groups had a CFS score of 9 ('Terminally ill').

Compared to non-frail patients (CFS 1–4), frail patients (CFS 5–9) were more likely to be female ($p < .001$), lower educated ($p = .027$), divorced or widowed ($p < .001$), living alone or in a healthcare facility ($p < .001$) and had more often a chronic diagnoses ($p < .001$). Besides, frail patients had more unplanned ICU admissions ($p < .001$), were less often mechanically ventilated ($p < .001$), had longer ICU LOS ($p = .032$), and a nursing home as discharge location ($p = .039$) (Table 1). No significant differences were found in age, APACHE IV score and hospital LOS.

Table 1
Characteristics of all included patients, and non-frail and frail patients.

	Total group (n = 1300)		Non-frail (CFS 1-4) (n = 1147)		Frail (CFS 5-9) (n = 153)		P-value
Patient characteristics							
CFS score at baseline, median [IQR]	3	[2–4]	2	[2–3]	6	[5–7]	<0.001*
Age, mean (SD) in years	61.4	(14.9)	61.4	(14.7)	61.0	(16.1)	0.743
Gender, n (%)							
• Male	843	(64.8)	766	(66.8)	77	(50.3)*	<0.001*
• Female	457	(35.2)	381	(33.2)	76	(49.7)*	
Education, n (%)							
• Low	414	(32.4)	351	(31.1)	63	(42.0)*	0.027*
• Middle	552	(43.2)	495	(43.9)	57	(38.0)	
• High	312	(24.4)	282	(25.0)	30	(20.0)	
Marital status, n (%)							
• Single	217	(16.9)	188	(16.6)	29	(19.2)	<0.001*
• Married	896	(69.7)	810	(71.4)	86	(57.0)	
• Divorced	72	(5.6)	57	(5.0)	15	(9.9)*	
• Widowed	101	(7.9)	80	(7.0)	21	(13.9)*	
Household composition, n (%)							
• Alone	198	(15.5)	164	(14.5)	34	(22.8)*	<0.001*
• With someone else[a]	1059	(82.9)	956	(84.7)	103	(69.1)	
• Healthcare facility	21	(1.6)	9	(0.8)*	12	(8.1)*	
One or more chronic diagnosis[b], n (%)							
• No	963	(74.1)	887	(77.3)	76	(49.7)*	<0.001*
• Yes	337	(25.9)	260	(22.7)*	77	(50.3)*	
ICU/ clinical characteristics							
Admission type, n (%)							
• Elective surgical	841	(64.7)	767	(66.9)	74	(48.4)*	<0.001*
• Medical	307	(23.6)	250	(21.8)	57	(37.3)*	
• Acute surgical	152	(11.7)	130	(11.3)	22	(14.4)	
Planned admission, n (%)							
• No	447	(34.4)	375	(32.7)	72	(47.1)*	<0.001*
• Yes	853	(65.6)	772	(67.3)	81	(52.9)	
APACHE IV score, mean (SD)	54.1	(21.2)	53.9	(21.5)	55.4	(18.9)	0.425
Mechanical ventilation (MV)							
• No	393	(30.2)	327	(28.5)	66	(43.1)	<0.001*
• Yes	907	(69.8)	820	(71.5)	87	(56.9)	0.098
Days of MV, median [IQR]	1	[0–2]	1	[0–2]	1	[0–2]	
ICU LOS, days, median [IQR]	1	[1–2]	1	[1–2]	1	[1–3]	0.032*
Hospital LOS, days, median [IQR]	9	[6–15]	9	[6–15]	10	[6–22]	0.096
Discharge location, n (%)							
• Home	891	(82.0)	802	(82.9)	89	(74.8)	0.039*
• Rehabilitation centre	92	(8.5)	77	(8.0)	15	(12.6)	
• Nursing home	24	(2.2)	18	(1.9)	6	(5.0)*	
• Other	79	(7.3)	70	(7.2)	9	(7.6)	
Hospital mortality, n (%)	6	(0.5)	5	(0.4)	1	(0.7)	0.529
One year mortality, n (%)	116	(8.9)	92	(8.0)	24	(15.7)	0.003*

cardiovascular insufficiency, respiratory insufficiency, COPD, chronic dialysis or renal insufficiency.
[a] With someone else: partner, children, parents, etc.
[b] Chronic diagnosis are immunological insufficiency, AIDS, haematological malignancy, metastatic neoplasm, cirrhosis,
* Significant differences in characteristics between patients who are non-frail and frail. Data are based on the baseline questionnaire and patient's electronic health record.

3.3. Changes in frailty during 12 months after ICU admission

3.3.1. Patients with an unplanned ICU admission

Frailty levels changed significantly after ICU admission: CFS median baseline scores increased from 2 [IQR 2–4] to 5 [IQR 3–6] at hospital discharge, and decreased to 3 [IQR 2–5] after three months and 12 months [IQR 2–4]. The percentage of frail patients (CFS score of 5–9) increased from 16% at ICU admission to 53% at hospital discharge, and decreased to 18% and 10% at three and 12 months, respectively (Supplement 6). After 12 months, 23% of the patients were less frail, 42% more frail and 35% experienced the same frailty level as before the ICU admission (Supplement 7a and 7b). Changes in frailty differed between frail and non-frail patients: the more frail patients were at baseline, the more they improved during the next 12 months (Figs. 2a and 3a). After 12 months, 11% of the non-frail patients transitioned to the frail category, whereas 46% of the frail patients transitioned to the non-frail category.

3.3.2. Patients with a planned ICU admission

Frailty levels in patients with a planned ICU admission changed as well. Although their median CFS baseline score was higher (3 [IQR 2–3.5]) compared to patients with an unplanned admission, they were less frail in the months following ICU admission: 4 [IQR 3–5] at hospital discharge, 3 [IQR 2–3] after three months, and 2 [IQR 2–3] after 12 months. The percentages of frail patients was lower as well: 10% at baseline, 32% at hospital discharge, and 8% and 4% at three and 12 months respectively (Supplement 6). After 12 months, 32% of the patients were less frail, 27% more frail, and 41% experienced the same level of frailty as before ICU admission (Supplement 7a and 7c). Like the unplanned admitted patients, patients with a higher baseline score (indicating being more frail) were more likely to improve during the next 12 months (Fig. 2b and 3b). Of the non-frail patients, 5% transitioned to the frail category, whereas of the frail patients, 80% transitioned to the non-frail category.

Differences in frailty changes were also seen in several subgroups, for example in gender, education level, admission types and ICU LOS (Supplement 8).

3.4. Factors associated with changes in frailty

3.4.1. Patients with an unplanned ICU admission

The only factor significantly associated with being *less frail* after 12 months, was a higher frailty score at baseline ($b = -634$; $p < .001$) (Table 2). Factors that were significantly associated with being *more frail*, were older age ($b = 0.019$; $p = .013$), longer hospital LOS ($b = 0.022$; $p = .001$), and being discharged to a revalidation centre ($b = 0.630$; $p = .020$).

3.4.2. Patients with an planned ICU admission

Factors significantly associated with being *less frail* after 12 months, were a higher frailty baseline score ($b = -0.756$; $p < .001$), male sex ($b = -0.207$; $p = .045$), higher education level ($b = -0.447$; $p < .001$) and mechanical ventilation ($b = -0.338$; $p = .002$ (Table 2). Factors that were significantly associated with *being more* frail at 12 months, were longer ICU ($b = 0.035$; $p = .036$) and hospital LOS ($b = 0.019$; $p = .010$), and being discharged to a nursing home ($b = 1.367$; $p = .005$) or another location ($b = 0.364$; $p = .046$).

The variables in both models explained 49% of the variance in frailty change.

Box 1. Examples of patients whose frailty level was declined, recovered or improved after 12 months.

Declined

A married man, in his sixties, with a middle level of education, was admitted to the ICU after a planned thoracotomy for oesophageal cancer. His APACHE IV score was 52. He was mechanically ventilated on the ICU for 2 days, and stayed 13 days in the hospital. He was very fit before ICU admission (CFS = 1), but vulnerable at hospital discharge (CFS = 4). Although he became less frail in the following months, he became terminally ill 12 months after ICU admission (CFS = 9).

Recovered

A young, low educated, unmarried woman, was admitted to the ICU after a planned craniotomy. Her APACHE IV score was 29. She stayed 1 day in the ICU without mechanical ventilation, and 5 days in the hospital. Before ICU admission she was very fit (CFS =1). At hospital

Table 2
Factors associated with changes in frailty scores for patients with an unplanned and planned ICU admission.

	Unplanned ICU admission ($n = 232$)				Planned ICU admission ($n = 494$)			
	B	SE	95% CI for B	P	B	SE	95% CI for B	P
Constant	0.994	0.655	[−0.30; 2.29]	0.131	1.622	0.357	[0.92; 2.32]	<0.001*
CFS baseline (T0)	−0.634	0.059	[−0.75; −0.52]	<0.001*	−0.756	0.038	[−0.83; −0.68]	<0.001*
Age	0.019	0.008	[0.00; 0.03]	0.013*	0.009	0.005	[0.00; 0.02]	0.052
Gender (female ref)								
• Male	−0.275	0.178	[−0.63; 0.08]	0.124	−0.207	0.103	[−0.41; −0.00]	0.045*
Education (low ref)								
• Medium	0.0530	0.2110	[−0.36; 0.47]	0.8040	−0.144−	0.1120	[−0.36; 0.08]	0.199
• High	.017	.229	[−0.44; 0.47]	.941	0.447	.125	[−0.69; −0.20]	<0.001*
Marital status (unmarried ref)								
• Married	−0.408−	0.3080	[−1.02; 0.20]	0.1860	0.1580	0.1700	[−0.18; 0.49]	0.3540
• Divorced	0.082−	.4250	[−0.92; 0.76]	.8480	.239−	.2640	[−0.28; 0.76]	.3650
• Widowed	0.718	.499	[−1.70; 0.27]	.152	0.518	.280	[−1.07; 0.03]	.065
Household composition (alone ref)								
• Together	−0.066	0.3700	[−0.80; 0.66]	0.8580	−0.2980	0.2260	[−0.74; 0.15]	0.1880
• Healthcare facility	1.296	.675	[−0.04; 2.63]	.056	.721	.784	[−0.82; 2.26]	.358
Chronic diagnosis (no ref)								
• Yes	−0.162	0.217	[−0.59; 0.27]	0.457	0.174	0.113	[−0.05; 0.40]	0.125
Admission type (elective surgical)								
• Medical	0.4170	0.3770	[−0.33; 1.16]	0.2700	−0.600−	0.3610	[−1.31; 0.11]	0.0970
• Acute surgical	.179	.393	[−0.60; 0.95]	.649	0.102	.467	[−1.02; 0.82]	.828
APACHE IV score	−0.003	0.003	[−0.01; 0.00]	0.356	0.003	0.004	[−0.00; 0.01]	0.448
Mechanically ventilated (no ref)								
• Yes	−0.294	0.198	[−0.69; 0.10]	0.140	−0.338	0.110	[−0.55; −0.12]	0.002*
ICU LOS	0.009	0.015	[−0.02; 0.04]	0.532	0.035	0.017	[0.00; 0.07]	0.036*
Hospital LOS	0.022	0.007	[0.01; 0.04]	0.001*	0.019	0.007	[0.00; 0.03]	0.010*
Discharge location (home ref)								
• Revalidation centre	0.6300	0.2690	[0.10; 1.16]	0.020*0	−0.448	0.2730	[−0.99; 0.01]	0.1010
• Nursing home	.6630	.4820	[−0.29; 1.61]	.1710	1.3670	.4790	[0.43; 2.31]	.005*0
• Other	.453	.300	[−0.14; 1.05]	.133	.364	.182	[0.01; 0.72]	.046*

Abbreviations: B, unstandardized regression coefficients; CI, confidence interval; CFS, clinical frailty scale; SE, standard error; Ref, reference group.
Linear regression model, with the CFS mean change score (T0-T3) as outcome. Data are unstandardized regression coefficients with 95% confidence intervals and p-values (*statistically significant). Note: negative regression coefficients indicate patients become less frail, positive regression coefficient indicate patients become more frail.

discharge she was more frail (CFS = 3), but after three months she was already very fit again.

Improved

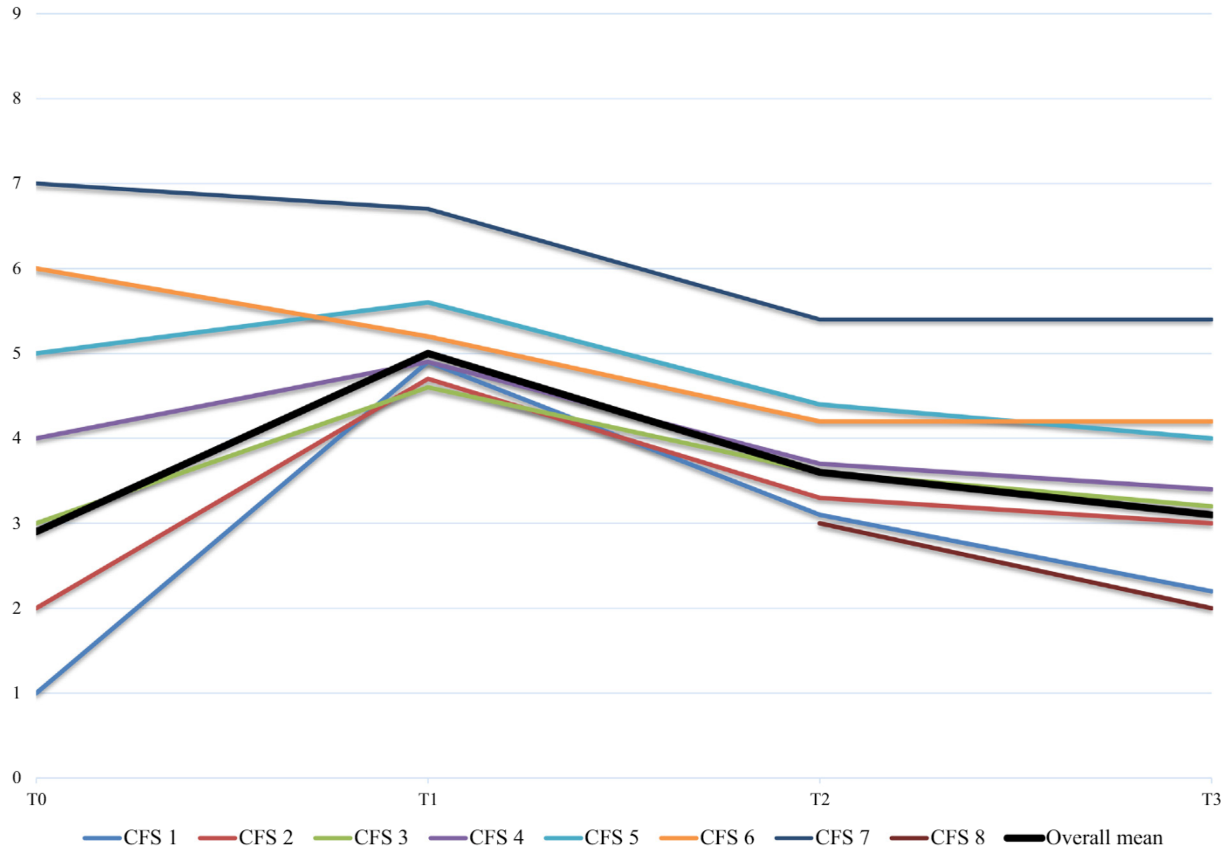
A high educated married man, in his fifties, was unexpectedly admitted to the ICU due to an endocrine and metabolic disorder. His APACHE IV score was 52. He spent one day on the ICU, without mechanical ventilation, and 21 days in the hospital. Before ICU admission he was severely frail (CFS = 8), but improved significantly in the months after discharge. After 3 and 12 months his frailty scores were respectively 3 and 2.

4. Discussion

In this prospective cohort study, including 1300 patients, we found that 16% of the unplanned and 10% of the planned patients were frail before their admission. Frail patients were more likely to be female, lowered educated, divorced or widowed, diagnosed with a chronic condition, and living alone or in a healthcare facility compared to non-frail patients. Additionally, frail patients had a longer ICU LOS and were more frequently discharged to a nursing home facility. After ICU admission the frailty levels changed: patients were more frail at hospital discharge, and less frail in the following months, although opposite changes were seen between frail and non-frail patients. Different patterns were also seen between patients with an unplanned and planned ICU admission: although patients with an unplanned admission were less frail before admission, they were more frail in the following months compared to patients with a planned admission. Besides, almost 50% of the patients with an unplanned admission and 25% of the patients with a planned admission were more frail after 12 months. Factors associated with changes in frailty differed as well between both groups. In patients with an unplanned admission was a higher CFS baseline score associated with being becoming *less* frail, and were older age, a longer ICU LOS, and being discharged to a revalidation centre associated with becoming *more* frail after 12 months. In patients with a planned admission were a higher CFS baseline score, being highly educated, and mechanical ventilation associated with becoming *less* frail. Longer ICU and hospital LOS, and being discharged to a nursing home were associated with being *more* frail.

Since a few years is frailty recognized as an important prognostic determinant for critically ill patients, and are associations with adverse short and long-term outcomes examined [7,8,24]. Frailty rates in patients being admitted to the ICU differ considerably between studies, ranging from 13 to 53% [25]. In a meta-analysis of 10 observational cohort studies including patients admitted to the ICU [7], a pooled frailty prevalence of 30% was found. This is higher compared to the rates found in our study (16% and 10% for the unplanned and planned patients, respectively), which is probably due to the exclusion of terminally ill patients in our study. Nevertheless, the differences between frail and non-frail patients found in our study, are consistent with previous studies, showing that frail patients at ICU admission are significantly more often female [9,12,26–29], widowed [9,12], lower educated [9,12,26,27], living with support or in a healthcare facility [9,12,26,30], have more often a medical ICU admission [9,27–29,31] and a nursing home as discharge location [7,27,29,30]. Although it might be expected that frail patients are older, have higher APACHE scores and longer hospital length of stay [9,31], we did not find significant differences between frail and non-frail patients, although contradictory findings are reported by other studies [26,29,30,32].

Changes in frailty among critically ill patients over time have not been examined before. Nonetheless, changes in frailty among community-dwelling older people have extensively been examined,



Number of patients per time point per baseline category: T0,T1,T2,T3

CFS 1: 97, 86, 72, 62
CFS 2: 138, 122, 97, 87
CFS 3: 92, 78, 64, 56
CFS 4: 48, 42, 33, 29
CFS 5: 18, 17, 13, 8
CFS 6: 27, 21, 17, 12
CFS 7: 26, 22, 16, 12
CFS 8: 1, 0, 1, 1
CFS 9: 0

T0: before ICU admission, T1: at hospital discharge, T2: three months after ICU admission, T3: 12 months after ICU admission

a

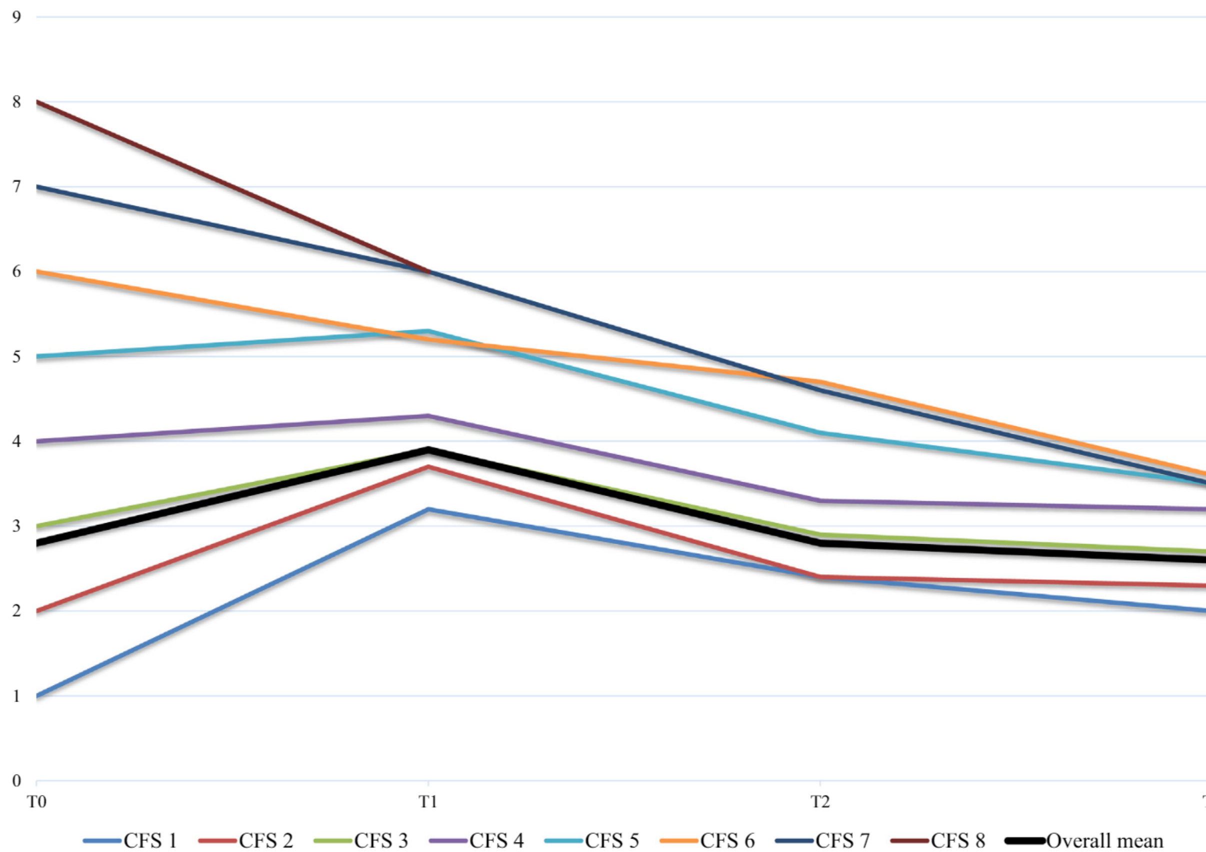
Fig. 2. a) Mean CFS scores over time indicated per baseline CFS score: unplanned ICU admission.

corroborating as well that frailty is a dynamic state. A meta-analysis, including >42.000 participants from 16 studies, analysed transitions between frailty states, and showed that over a period of four year, frailty worsened in 29%, maintained the same in 57%, and improved in 14% participants [18]. In our study, patients became more frail at hospital discharge and less frail in the following months, although differences were seen between patients with an unplanned and planned ICU admission: 42% of the patients with an unplanned admission were more frail after one year, compared to 27% of the patients with a planned admission. These differences are not remarkable. A study that compared older patients admitted to the ICU after acute (unplanned admission) versus elective surgery (planned admission), showed that elective surgery patients are less sick, have shorter ICU LOS, lower mortality and better outcomes compared to patients after acute surgery [33].

Factors associated with changes in frailty in non-ICU patients, are age [34,35], gender [35,36], education level [34,35] and hospital LOS [36]. Other interesting reported factors, not investigated in our study, are limitations in daily living, low albumin levels, lower cognition, loss of vision, polypharmacy, smoking, obesity, and conditions such as COPD, diabetes, cancer, cardiovascular diseases, stroke and osteoarthritis [34,35,37]. Remarkably, we found that frail patients were *more* likely to improve over time than non-frail patients, whereas other studies suggested that frail patients were *less* likely to re-achieve their baseline function [22] and were more likely to die [36], while non-frail patients tended to remain healthy [36] and recovered completely from acute illness [22]. This sounds more reasonable, and this contradictory finding could be a result of the exclusion of terminally ill patients in our study and the complete case analysis, in which the non-survivors and non-responders, with both higher frailty rates before ICU admission, were not included.

5. Implications

Frailty is common among ICU patients [7,24,29], and unmistakably associated with adverse health outcomes, prolonged recovery, higher mortality and higher healthcare utilizations [7,9,12,27]. Screening for frailty in ICU patients, to identify and recognize those who are at risk, will increase clinical awareness of patient's vulnerability, stratification of patients at risk, prognostication, and informed decision making [10,15,27,29,38–41]. In addition, it will lead to better informed patients and families, regarding the prognosis for survival, expectations of recovery, and expected resource use [22,41]. Although there is no consensus on which screening instrument to use in the ICU [7,8,25,39], since commonly used instruments are not feasible in the IC, due to time constraints and measurements impossible to perform [7,30,39,40], simple and rapid frailty screening instruments, such as the CFS, can be used [25,39,42,43]. However, frailty screening instruments should be robust



Number of patients per time point per baseline category: T0,T1,T2,T3
CFS 1: 109, 100, 90, 74
CFS 2: 296, 272, 241, 212
CFS 3: 235, 223, 192, 160
CFS 4: 132, 115, 97, 88
CFS 5: 38, 34, 29, 23
CFS 6: 19, 18, 13, 11
CFS 7: 22, 19, 16, 11
CFS 8: 2, 0, 1, 1
CFS 9: 0
T0: before ICU admission, T1: at hospital discharge, T2: three months after ICU admission, T3: 12 months after ICU admission

b

Fig. 2 (*continued*).

and properly validated [25]. The validity and reliability of the CFS should be further tested and improved [39], for example by the comparison with a gold standard, the comprehensive geriatric assessment carried out by a specialist in geriatric medicine [24]. Additionally, the CFS is a subjective frailty assessment, often relying on information from proxies, which can lead to an underestimation of frailty [25,39,40]. In two inter-reliability studies, an agreement in frailty assessment was found in half of the cases [30,44]. Clear instructions, simplifying the wording, and training of ICU professionals, might improve the reliability. Additionally, we should keep in mind that screening can cause false reassurance, whereby identification of non-frailty could be wrongly interpreted as indicating they are less likely to develop frailty in the future. In our study we showed that many patients who were identified as non-frail at ICU admission, were *more* frail after one year, especially in patients with an unplanned admission.

It is important that critical care healthcare professionals are aware that the diminished reserve in frail patients may increase the adverse effects of routine critical care treatment, such as bed rest, polypharmacy, sedation and mechanical ventilation [7,13], and that the reduced resilience in frail patients may make their recovery more difficult and prolonged [7]. By efficient weaning strategies [8], minimization of unnecessary sedation [7–10], screening for delirium [8,9], reduction of polypharmacy [9,43], adequate nutritional support, [4,7,9,10,43,45], cognitive training [4,45] and early mobilization and exercises [4,7–9,43,45,46] frailty progression among ICU patients could be prevented and positive outcomes maximized.

6. Limitations

This study has certain limitations. First, our study was conducted in one university medical centre, in which the majority of the ICU patients were admitted after elective surgery. Because of this case-mix, and consequently the limited generalizability of the findings to other ICUs, we separated the analysis for patients with an unplanned and planned ICU admission. Second, selection bias is likely due to the considerable number of patients lost to follow-up, which is a major challenge in long-term outcome studies in critical care [47,48]. Although loss to follow-up cannot be eliminated [47], we tried to minimize it by the use of telephone and e-mail reminders, providing patients the option to fill in the questionnaire on paper or online, and ask proxies to fill in the questionnaires when patients were unable to do it. Third, 20% of the baseline CFS score were completed by proxies instead of the patients themselves, especially in patients with an unplanned admission (40% compared to 10% in the planned admissions). Because family members tend to underestimate the frailty levels of their loved one [40], CFS scores could be underrated. Fourth, bias of the results is also possible due to our decision for the complete-case analysis. There is a lack of consensus on how to deal in statistical analyses with patients who die

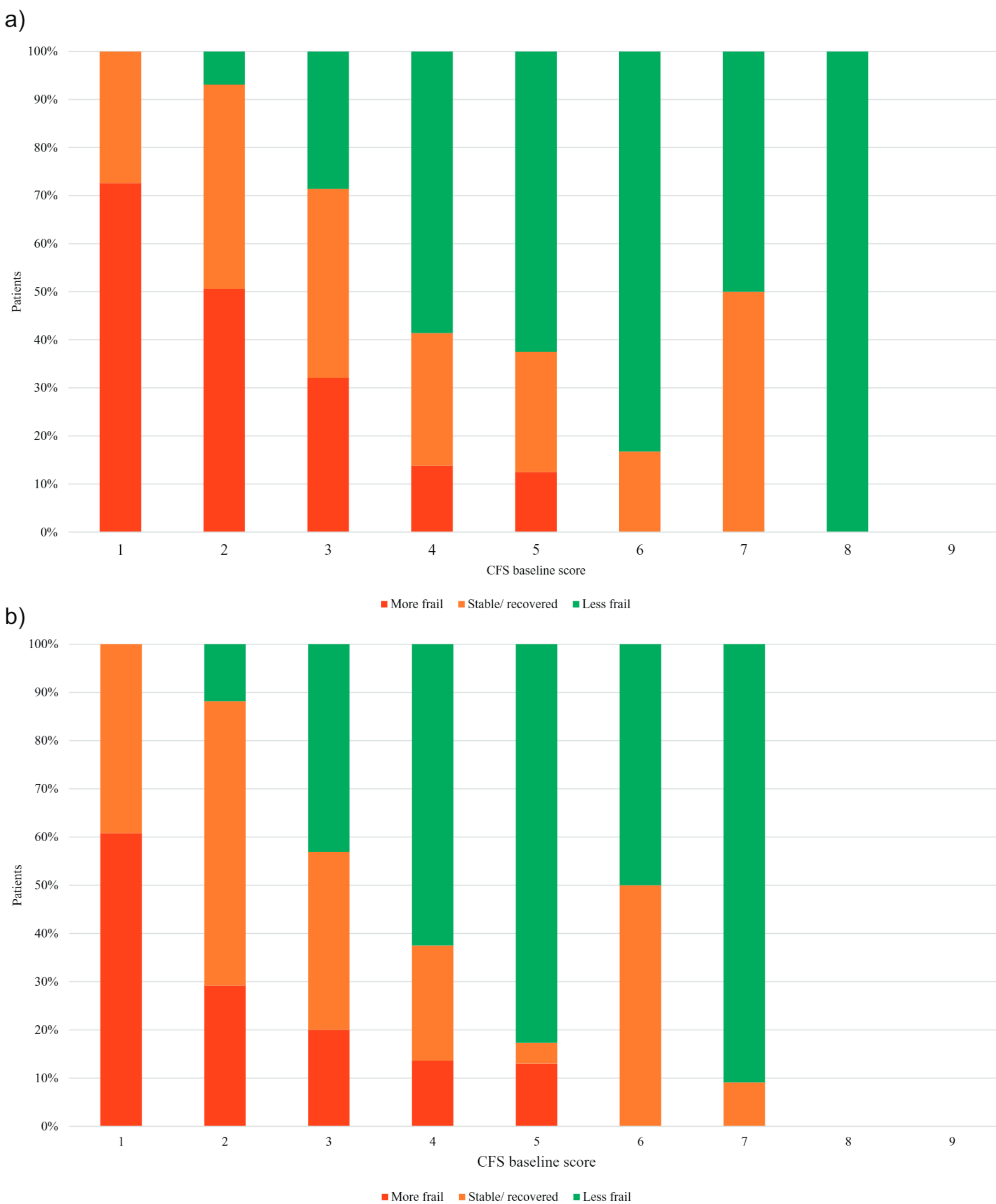


Fig. 3. b) Frailty status 12 months after ICU admission compared to the frailty status before the ICU admission (indicated per CFS baseline score): planned ICU admission.

during follow-up, as they could not be considered as a missing [49]. Like most studies, we decided to exclude them from the analysis [49]. By describing the characteristics and differences between the complete-case patients, the non-survivors and non-responders, we tried to get insight into the magnitude and direction of the selection bias. Significant higher baseline CFS scores were found in the non-survivors, which could explain the improvements in frailty in especially the patients who were frail at ICU admission. And fifth, the explored factors in this study that were associated with changes in frailty, were mainly patient demographic factors. Unfortunately, we were not able to include more clinical factors such as delirium, sepsis, use of sedatives and other medications, because these data were not available. It is likely that these factors might have an influence on the changes in frailty as well.

7. Conclusion

In conclusion, frailty levels changed following ICU admission, with higher frailty levels at hospital discharge, and lower levels at 12 months. After one year, 42% of the patients with an unplanned admission and 27% of the patients with a planned admission were more frail. For both groups were older age, longer hospital length of stay, and discharge location associated with being more frail. In the planned ICU patients were male sex, higher education level and mechanical ventilation associated with being less frail. Insight in the associated factors will help to identify patients at risk, and may guide in clinical decision making and informing patients and their family members.

Disclosure

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Declaration of Competing Interest

None.

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Appendix A. Suppplementary data

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